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NEW DRUGS

Safinamide mesylate, Brodalumab, Guselkumab, and Abaloparatide

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Antiparkinson agent

Safinamide mesylate (Xadago—Newron) is the third monoamine oxidase type B (MAO-B) inhibitor to be marketed in the United States for the treatment of patients with Parkinson disease, joining selegilene (e.g., Eldepryl) and rasagiline (Azilect). By inhibiting MAO-B activity, these agents reduce the catabolism of dopamine, resulting in increased dopamine concentrations and dopaminergic activity in the brain. The inhibition of MAO-B activity by safinamide is considered to be reversible, whereas selegilene and rasagiline irreversibly inhibit MAO-B activity. However, whether this distinction is of clinical importance is not known.

The selective action of these 3 drugs in inhibiting MAO-B has been suggested to decrease the risk of adverse events and drug interactions associated with the use of nonselective MAO inhibitors (e.g., phenelzine, tranylcypromine) that also inhibit MAO-A. However, the selectivity of the action is related to the dosage of the medications, and the experience of patients treated with the same dosage may vary widely. Accordingly, many of the warnings and precautions for the nonselective MAO inhibitors should also be observed for the selective MAO-B inhibitors, including safinamide.

Safinamide is specifically indicated as adjunctive treatment to levodopa/carbidopa (e.g., Sinemet) in patients with Parkinson disease experiencing "off" episodes (periods during treatment when there is an increase in Parkinson symptoms, such as tremor and difficulty walking). Although rasagiline also has labeled indications as monotherapy, as well as adjunctive treatment without levodopa, it is usually used with levodopa.

The effectiveness of safinamide was evaluated in 2 placebo-controlled studies in patients also being treated with levodopa/carbidopa, dopamine agonists, catechol *O*-methyl transferase inhibitors, anticholinergics, and amantadine. The primary measure of effectiveness was the change from baseline in "on" time without troublesome dyskinesia. In both studies, safinamide significantly increased "on" time compared with placebo, and this was accompanied by a similar significant reduction in "off" time as well as a reduction in the Unified Parkinson Disease Rating Scale Part III scores that were assessed during "on" time.

Safinamide has not been shown to be effective as monotherapy for the treatment of patients with Parkinson disease. In addition to its use in the treatment of Parkinson disease, selegilene is used in a transdermal system (Emsam) for the treatment of patients with major depressive disorder. However, this is not a labeled indication for safinamide.

The adverse events most often experienced in the clinical studies of safinamide (and their incidence with the recommended maintenance dosage of 100 mg daily) include dyskinesia (17%), fall (6%), nausea (6%), and insomnia (4%). The new agent may cause dyskinesia or exacerbate preexisting dyskinesia, and reducing the dosage of levodopa or other dopaminergic treatment should be considered.

Patients treated with dopaminergic medications, including the MAO-B inhibitors, have experienced complications for which precautions must be observed with the use of safinamide. Some patients have experienced sleep attacks or sudden onset of sleep and fallen asleep while engaged in daily activities (e.g., driving). The use of the drug should usually be discontinued if such experiences occur, but if treatment is continued, patients should be advised to avoid driving and other potentially dangerous activities. These medications have also been reported to cause problems with impulse control and compulsive behaviors that may include intense urges to gamble, spend money, and binge eat and increased sexual urges. Patients with a major psychotic disorder should ordinarily not be treated with safinamide. Treatments for psychosis that antagonize the effects of dopaminergic medications may exacerbate the symptoms of Parkinson disease.

Safinamide may cause hypertension or exacerbate existing hypertension, and patients must be monitored accordingly. Concurrent use with another MAO inhibitor, including the antibacterial agent

The **New Drugs** column informs readers about new chemical and biologic entities approved for marketing by the U.S. Food and Drug Administration. The column is written by Contributing Editor Daniel A. Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, PA.

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linezolid, is contraindicated because of the potential for a hypertensive crisis. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with another MAO inhibitor. Because isoniazid has some MAO-inhibiting activity, the concurrent use of safinamide must be closely monitored. MAO in the gastrointestinal tract and liver is primarily MAO-A which protects against pressor effects of exogenous amines, such as tyramine, that may be present in large amounts in aged, fermented, cured, smoked, and pickled foods (e.g., aged cheese). Patients should be advised to avoid foods containing a large amount of tyramine while being treated with safinamide. The concurrent use of safinamide with certain sympathomimetic medications (amphetamine, methylphenidate, and their derivatives) is contraindicated. If safinamide is used concurrently with other prescription or nonprescription sympathomimetic medications, including oral, nasal, or ophthalmic decongestants and cold remedies, caution must be observed and patients monitored for hypertension.

Because of the risk of serotonin syndrome, the concomitant use of safinamide with certain serotonergic drugs, including serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine), tricyclic, tetracyclic, or triazolopyridine antidepressants, cyclobenzaprine, or St. John's wort is contraindicated. Although not specifically contraindicated, concurrent use of safinamide with a selective serotonin reuptake inhibitor (e.g., fluoxetine, sertraline) is best avoided. Serious reactions have also resulted from the concomitant use of safinamide with opioid drugs (e.g., meperidine, methadone, propoxyphene, tramadol), and their concurrent use is contraindicated. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with a serotonergic drug or opioid. The use of safinamide with dextromethorphan is also contraindicated because of reports of psychosis or bizarre behaviors in patients taking other MAO inhibitors and dextromethorphan.

There have been reports of retinal degeneration and other ocular adverse events when safinamide was used in animal studies. Patients with a history or family history of retinal or macular disease should be monitored for visual changes.

Safinamide is classified in pregnancy category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. In nursing mothers, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of safinamide in pediatric patients have not been established.

After oral administration, the absolute bioavailability of safinamide is 95%, and it may be administered without regard to meals. The drug is extensively metabolized to inactive metabolites, and approximately 75% of a dose is recovered in the urine in the form of metabolites. The pharmacokinetics of safinamide are not affected by impaired renal function. However, it should be used in a reduced dosage in patients with moderate hepatic impairment, and its use is contraindicated in patients with severe hepatic impairment.

Safinamide and its major metabolite may inhibit intestinal breast cancer resistance protein (BRCP) and could increase plasma concentrations of BRCP substrates, such as methotrexate, imatinib, and rosuvastatin. Concurrent use should be closely monitored for increased activity and risk of the BRCP substrates.

The recommended starting dosage of safinamide is 50 mg once a day at the same time each day. After 2 weeks, the dosage may be increased to 100 mg once a day, based on individual need and tolerability. If a dose is missed, the next dose should be taken at the same time the next day. In patients with moderate hepatic impairment, the maximum recommended dosage is 50 mg once a day. If a patient receiving treatment with this dosage experiences worsening of hepatic impairment, the drug should be discontinued.

A symptom complex resembling neuroleptic malignant syndrome has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone. If treatment with safinamide is to be discontinued, the dosage should be decreased to 50 mg once a day for 1 week before stopping therapy.

Safinamide mesylate is supplied in tablets in quantities equivalent to 50 mg and 100 mg safinamide free base.

Agents for psoriasis

Certain naturally occurring interleukins (ILs) have been identified as having a role in the occurrence and worsening of psoriasis, and the development of IL receptor inhibitors has been a focus of recent research efforts. Ustekinumab (Stelara) inhibits IL-12 and IL-23 and was the first IL inhibitor to be approved for the treatment of patients with psoriasis. IL-17A is another interleukin that is present in elevated concentrations in psoriatic plaques, and the IL-17A inhibitors secukinumab (Cosentyx) and ixekizumab (Taltz) were marketed in 2015 and 2016, respectively, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Secukinumab has also been subsequently approved for the treatment of patients with psoriatic arthritis and ankylosing spondylitis, and ixekizumab has recently been approved for the treatment of patients with psoriatic arthritis. Two new IL inhibitors have been marketed in 2017 for the treatment of patients with psoriasis, and they are considered on an individual basis in the following discussions.

Brodalumab (Siliq—Valeant) is the third monoclonal antibody that acts as an IL-17A inhibitor and, like the other 2 agents, is administered subcutaneously. It is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. The labeling for secukinumab and ixekizumab does not include the limitation of reserving use of the drug for patients who have failed or lost response to other systemic therapies.

The effectiveness of brodalumab was demonstrated in 3 placebo-controlled studies that included more than 4000 participants. The primary end points were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to week 12 and an improvement in the Physician Global Assessment (PGA) to clear or minimal. Of the patients treated with brodalumab, 83% to 86% attained a PASI 75 response, compared with 3% to 8% of those who received placebo, and 37% to 44% treated with the new drug attained a PASI 100 response, compared with fewer